University of Szeged
Doctoral School of Pharmaceutical Sciences

Educational programme: Pharmaceutical Chemistry and Drug Research

Programme director: Prof. Dr. Ferenc Fülöp

Institute of Pharmaceutical Chemistry

Supervisors:

Prof. Dr. Ferenc Fülöp, Dr. Sándor Ötvös

Continuous-flow methodologies for copper-catalyzed reactions

Summary of PhD thesis

Ádám Georgiádes

Final examination committee:

Head:	Dr. László Lázár
Members:	Dr. György Dombi
	Dr. György Dormán

Reviewer committee:

Head:	Dr. György Dombi
Reviewers:	Dr. György Dormán
	Dr. György Túrós
Members:	Dr. György Szöllősi
	Dr. Attila Hunyadi

Szeged

2019

1. Introduction and aims

Continuous production is a long-established strategy in the industry: oil refining, synthetic fiber manufacturing, and papermaking have been applying uninterrupted methods for centuries. The application of continuous-flow (CF) processes in the synthetic chemistry appeared only two decades ago, offering significant advantages over the conventional segmented techniques. Owing to their technological possibilities, they allow simple, safe, and precise fine-tuning of the reaction conditions. Moreover, the enhanced heat and mass transfer provides an impaired level of reaction control. Flow chemistry also offers in-line analysis, purification, and even formulation. Thus, CF technology may serve as an avenue towards the technological revolution of chemical synthesis.

Since the first examples, CF synthesis methods have gone through an extraordinary progression. Due to their advantages over conventional techniques and applicability in difficult and sensitive reactions, CF methods became an impressive tool for synthetic chemistry and proved not to be only a transient vogue. The borderline between segmented and flow processes has become more apparent, making it straightforward to decide whether the application of a CF process is beneficial or unnecessary. Nowadays, performing the entire synthesis of complex compounds (such as APIs) as uninterrupted continuous-flow processes is an actual endeavor.

Our aim was to apply continuous-flow technology, focusing attention on copper-catalyzed reactions to explore otherwise hidden parameter spaces from classical batch syntheses and to develop efficient, selective, safe, and sustainable synthesis methods. Highlighting its applicability in organic chemistry, we investigated the CF technology in three reaction systems: (*i*) highly controlled synthesis of aryl azides and aniline derivatives from haloarenes; (*ii*) extension of the chemical parameter spaces for the oxidative homocoupling of aniline derivatives; (*iii*) two-step *in continuo* synthesis of 3,5-disubstituted pyrazoles. Each work represents a case study how CF processes can improve synthetic reaction technology.

2. Methods

Reagents and materials were commercially available and used as received. The synthesized compounds were separated and purified by column chromatography on silica gel. The compounds were characterized by NMR spectroscopy, mass spectrometry.

Reactions were carried out in “home-made” flow reactors consisting of HPLC pumps, stainless steel coils or stainless steel HPLC columns as the active reactor zone, stainless steel preheating coil and commercially available backpressure regulators. The parts of the system

were connected with stainless steel and PEEK capillary tubing. The stainless steel coil and the preheating coil were immersed in a heated oil bath.

3. Results and discussion

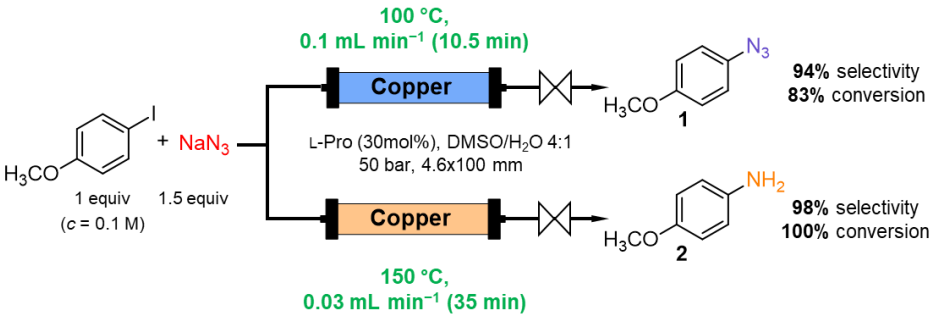
3.1 Controlled transformations of aryl halides

Selective synthesis of aryl azides and aniline derivatives was achieved in a continuous-flow system using the corresponding aryl halides as practical starting materials.

For the initial optimization study, the copper-catalyzed reaction of 4-iodoanisole with sodium azide was chosen as model reaction. Commercially available copper powder (<425 µm particle size) was employed as a cheap, readily available, non-toxic, and reusable catalytic source. The reaction conditions were carefully investigated to understand their role on product selectivity.

The investigation of the effect of the solvent, NaN_3 and auxiliaries, temperature and flow rates led to the conclusion that the product selectivity could be modified through fine-tuning the residence time and temperature. It was established that after copper-mediated halogen–azide substitution, the azide decomposition/reduction is also dependent on the presence of the catalytic metal.

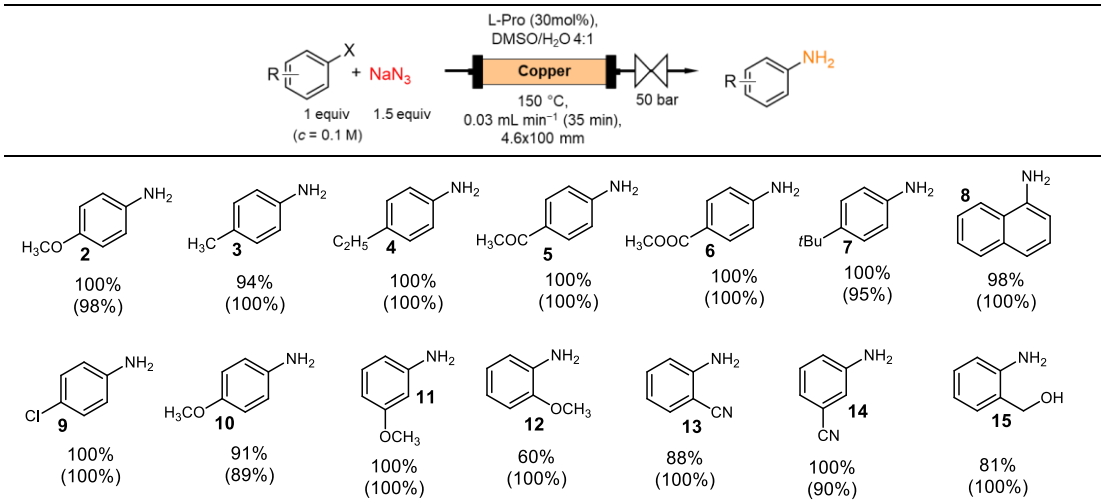
At the end of the optimization phase, two distinct parameter sets were specified for the selective synthesis of either azide **1** or amine **2** using 4-iodoanisole as common starting material and the same auxiliaries (Scheme 1).



Scheme 1. *Optimal reaction parameters for the diversity-oriented synthesis of 1-azido-4-methoxybenzene (**1**) and 4-methoxyaniline (**2**) from 4-iodoanisole as starting material*

Reaction conditions developed for the model reaction were subsequently utilized for the synthesis of a diverse set of aromatic amines **2-15** (Table 1). Both electron-donating and electron-withdrawing substituents were nicely tolerated, and anilines were formed in high conversion and with excellent chemoselectivity. Even ortho-substituted aryl bromides were successfully transformed into the desired derivatives.

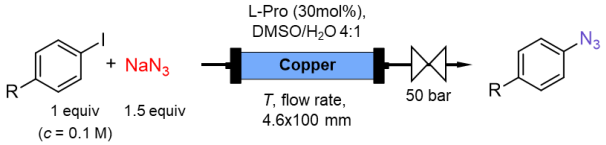
Table 1. *Continuous-flow synthesis of various aryl amines from aryl halides as starting materials*

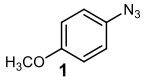
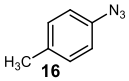
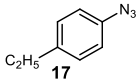
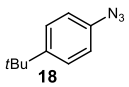
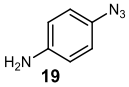


Conversions indicated under each compound, selectivities indicated in parentheses.

Synthetically more challenging aryl azides **1, 16-19** were prepared selectively with individual optimization of both the temperature and residence time for each substrate (Table 2). Minor differences in the substitution pattern of the haloarene led to notable changes in the reaction outcome.

Table 2. *Continuous-flow synthesis of various aryl azides from aryl halides as starting materials*



Entry	Product	Conditions	Conv.[a] (%)	Select.[a] (%)
1		100 °C, 0.1 mL min^{-1} (10.5 min)	83	94
2		100 °C, 0.1 mL min^{-1} (10.5 min)	89	11
3		120 °C, 0.15 mL min^{-1} (7.8 min)	87	65
4		120 °C, 0.2 mL min^{-1} (5.2 min)	78	90
5		140 °C, 0.15 mL min^{-1} (7.8 min)	96	16
6		100 °C, 0.1 mL min^{-1} (10.5 min)	70	36
7		120 °C, 0.2 mL min^{-1} (5.2 min)	82	82
8		100 °C, 0.1 mL min^{-1} (10.5 min)	77	79
9		100 °C, 0.15 mL min^{-1} (7.8 min)	65	80
10		120 °C, 0.2 mL min^{-1} (5.2 min)	90	71
11		120 °C, 0.25 mL min^{-1} (4 min)	71	85
12		140 °C, 0.25 mL min^{-1} (4 min)	88	61
13		80 °C, 0.05 mL min^{-1} (21 min)	80	75
14[b)]		100 °C, 0.1 mL min^{-1} (10.5 min)	62	100
15[b)]		100 °C, 0.05 mL min^{-1} (21 min)	86	100

[a] Determined by ^{1}H NMR spectroscopy of the crude material. [b)] Due to solubility issues DMSO/H_2O 5:1 was used as solvent.

3.2 New parameter spaces for the oxidative homocoupling of aniline derivatives

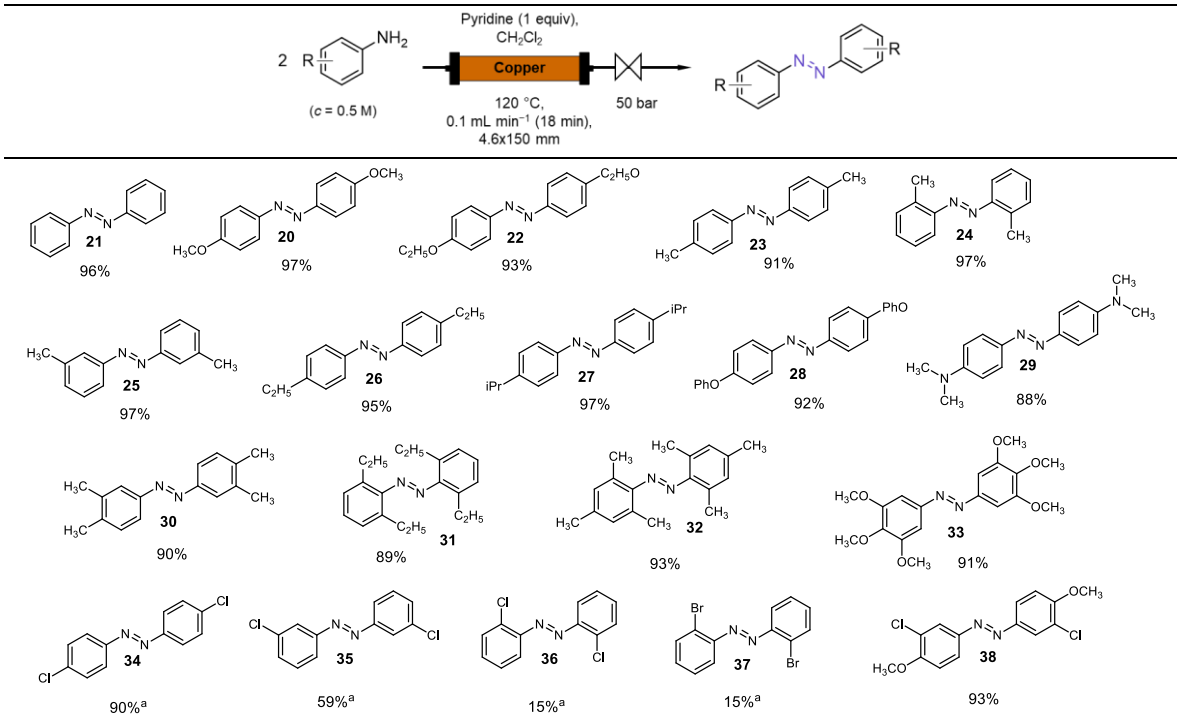
An efficient continuous-flow methodology was developed for the synthesis of aromatic azo compounds.

As model reaction for the optimization study, the oxidative homocoupling of *p*-anisidine was chosen. Commercially available copper powder (<425 μm particle size) was employed as catalytic source.

The novel process window of increased temperature and pressure ranges in combination with the application of overheated solvents revealed previously unknown correlations between reaction parameters that are not attainable in conventional flask chemistry and afforded a remarkable chemical intensification.

The scope of the method was successfully extended to the synthesis of aromatic azo compounds **21-38** (Table 3). Anilines bearing alkyl groups were nicely tolerated irrespective of the position of the substituent, and even anilines containing bulky moieties were converted quantitatively to the desired product. Di- and trisubstituted aniline derivatives showed excellent reactivities and the scope of the method was successfully extended to the reaction of even deactivated halogen-substituted anilines.

Table 3. *Exploring the reactivity of various aniline derivatives in oxidative homocoupling*



[a] 140 °C temperature. Isolated yields indicated under each compound.

The synthesis of the azobenzene **20** was scaled out simply as a function of the operation time. The 30-fold scale-out resulted 2.36 g of pure product, which corresponded to an overall yield of 86% and an excellent throughput of 0.32 g pure product per hour.

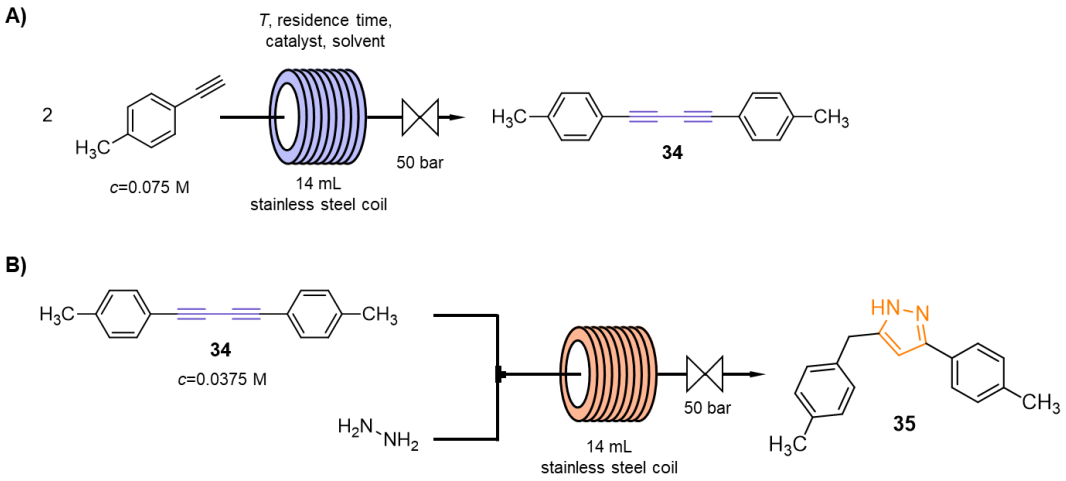
As part of a cooperation, the inherently basic character of a copper-containing layered double hydroxide (Cu(II)Fe(III)-LDH) was explored. The application of Cu(II)Fe(III)-LDH significantly boosted the reaction rates of the model reaction without any added base. As a result of the optimization process, complete conversion of the starting material was registered with 100% chemoselectivity.

The extensive investigation of the reactivity of the catalyst led to a set of variously substituted azobenzenes. The resulting azobenzenes were achieved with complete chemoselectivity and excellent yields in short process times even on preparative scales.

3.3 Multi-step synthesis of 3,5-disubstituted pyrazoles

A two-step continuous-flow process was developed for the synthesis of 3,5-disubstituted pyrazoles via sequential copper-mediated alkyne homocoupling and Cope-type hydroamination of the intermediary 1,3-dialkynes in the presence of hydrazine.

To explore and optimize the critical reaction parameters, the two reactions were investigated separately in a step-by-step manner. For the optimization of the 1,3-diyne synthesis, the catalytic dimerization of 4-ethynyltoluene was chosen as model reaction (Scheme 2 A). In case of the Cope-type hydroamination, the preformed 1,4-di-*p*-tolylbuta-1,3-diyne was utilized as model compound (Scheme 2 B).

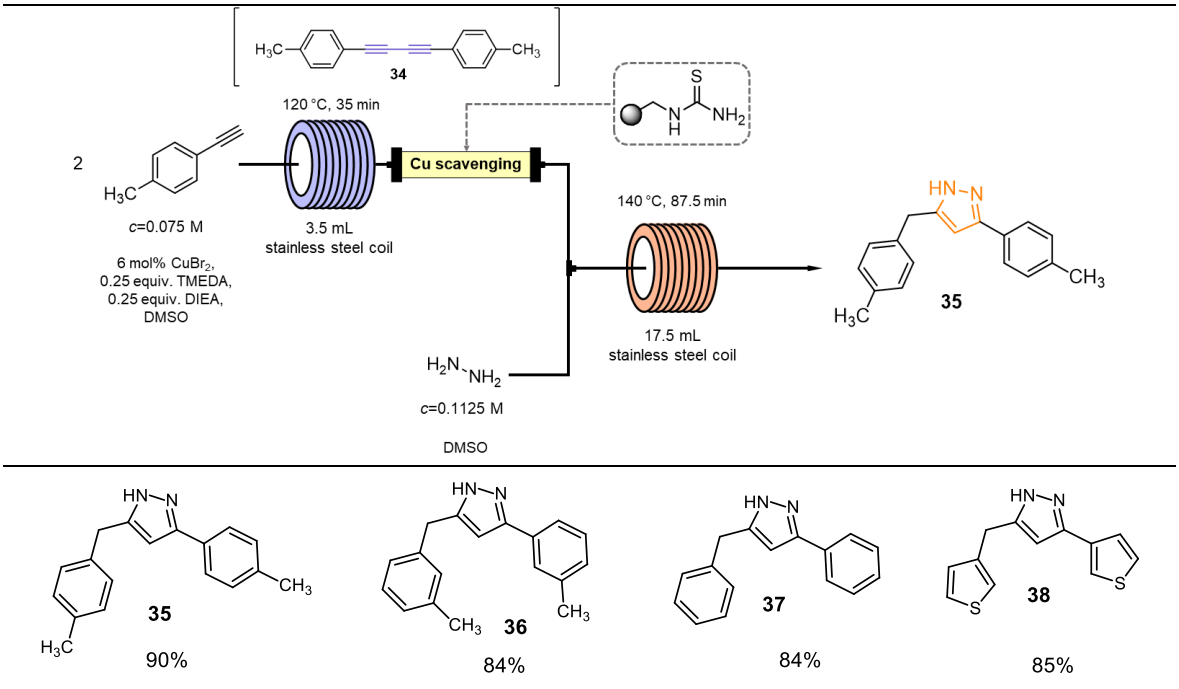


Scheme 2. *A) Oxidative homocoupling of 4-ethynyltoluene in a continuous-flow reactor B) Arrangement of the continuous-flow reactor for the hydroamination of 1,4-di-p-tolylbuta-1,3-diyne*

After having the necessary knowledge and optimal reaction conditions in hand, a multistep telescoped sequence was constructed where the 1,3-diyne intermediate was transformed directly into the corresponding pyrazole.

After an initial step-by-step optimization procedure, individual reaction components were organized into an uninterrupted flow sequence where, after in-line copper removal, the intermediary diynes were transformed further after being combined with a hydrazine stream (Table 4). Applying phenylacetylene, its methyl-substituted derivatives, and 3-ethynylthiophene as starting alkynes, excellent results were registered, the diyne formation took place quantitatively. As a result of the two-step synthesis, pyrazole products were achieved with full chemoselectivity, without side-product formation.

Table 4. *Exploring the reactivity of different alkynes in the telescoped alkyne homocoupling–hydroamination/cyclization process.*



Isolated yields indicated under each compound.

The transformation of 3-ethynylthiophene was scaled out simply by elevating the operation time. Thus, the previously optimized conditions were applied without any change in the alkyne, ligand, base or hydrazine concentration. The flow system was stable for an extended period of 16 h. 0.52 g of pure pyrazole **38** was isolated, which corresponded to an overall yield of 81%.

List of publications and lectures

Papers related to the thesis

I. Ádám Georgiádes, Sándor B. Ötvös, Ferenc Fülöp:
Exploring new parameter spaces for the oxidative homocoupling of aniline derivatives: sustainable synthesis of azobenzenes in a flow system
ACS Sustainable Chem. Eng. **2015**, *3*, 3388-3397. IF.: 5.267

II. Sándor B. Ötvös, Ádám Georgiádes, Rebeka Mészáros, Koppány Kis, István Pálinkó, Ferenc Fülöp:
Continuous-flow oxidative homocouplings without auxiliary substances: exploiting a solid base catalyst
J. Catal. **2017**, *348*, 90-99. IF.: 6.759

III. Ádám Georgiádes, Sándor B. Ötvös, Ferenc Fülöp:
Controlled transformations of aryl halides in a flow system: selective synthesis of aryl azides and aniline derivatives
Adv. Synth. Catal. **2018**, *360*, 1841-1849. IF.: 5.451 (2018)

IV. Sándor B. Ötvös, Ádám Georgiádes, Dániel Ozsvár, Ferenc Fülöp:
Continuous-flow synthesis of 3,5-disubstituted pyrazoles via sequential alkyne homocoupling and Cope-type hydroamination
RSC Advances, **2019**, *9,* 8197-8203. IF.: 3.049 (2018)

Other papers

V. Sándor B. Ötvös, Ádám Georgiádes, István M. Mándity, Loránd Kiss, Ferenc Fülöp:
Efficient continuous-flow synthesis of novel 1,2,3-triazole-substituted β-aminocyclohexanecarboxylic acid derivatives with gram-scale production
Beilstein J. Org. Chem. **2013**, *9*, 1508-1516. IF.: 2.801

VI. Sándor B. Ötvös, Gábor Hatoss, Ádám Georgiádes, Szabolcs Kovács, István M. Mándity, Zoltán Novák, Ferenc Fülöp:
Continuous-flow azide–alkyne cycloadditions with an effective bimetallic catalyst and a simple scavenger system
RSC Advances **2014**, *4*, 46666-46674. IF: 3.840

VII. Sándor B. Ötvös, Ádám Georgiádes, Mónika Ádok-Sipiczki, Rebeka Mészáros, István Pálinkó, Pál Sipos, Ferenc Fülöp:
A layered double hydroxide, a synthetically useful heterogeneous catalyst for azide–alkyne cycloadditions in a continuous-flow reactor
Applied Catalysis A **2015**, *501,* 63-73. IF: 4.012

Cumulative impact factor: 31.179

Scientific lectures related to the thesis

1. Georgiádes Ádám, Ötvös Sándor, Fülöp Ferenc:
   Aromás azovegyületek szelektív szintézise folyamatos áramú technikával
   MTA Heterociklusos Kémiai Munkabizottság Ülése, Balatonszemes, Hungary, 27-29 May 2015.
2. Georgiádes Ádám, Ötvös Sándor, Fülöp Ferenc:
   Gyógyszerkémiai paramétertér-bővítés áramlásos technikával – aromás azovegyületek szelektív szintézise
   Gyógyszerkémiai és Gyógyszertechnológiai Szimpózium, Herceghalom, Hungary, 17-18 September 2015.
3. Ádám Georgiádes, Sándor B. Ötvös, Rebeka Mészáros, Mónika Ádok-Sipiczki, István Pálinkó, Pál Sipos, Ferenc Fülöp
   A layered double hydroxide, an efficient heterogeneous catalyst for continuous-flow cycloadditions and oxidative homocouplings
   5th Conference on Frontiers in Organic Synthesis Technology, Budapest, Hungary, 21-23 October 2015.
4. Georgiádes Ádám, Ötvös Sándor, Mészáros Rebeka, Kis Koppány, Pálinkó István, Fülöp Ferenc:
   Környezettudatos oxidatív homokapcsolási reakciók áramlásos reaktorban hozzáadott bázis nélkül
   MTA Heterociklusos Kémiai Munkabizottság Ülése, Balatonszemes, Hungary, 18-20 May 2016.
5. Ádám Georgiádes, Sándor B. Ötvös, Rebeka Mészáros, Ferenc Fülöp
   In search of the right path – diversity-oriented aryl azide and arylamine synthesis in continuous-flow
   9th Asian-European Symposium on Metal-Mediated Efficient Organic Synthesis, Stockholm, Sweden, 4-7 September 2016.
6. Georgiádes Ádám, Ötvös Sándor, Fülöp Ferenc:
   Környezettudatos szintézismódszerek megvalósítása folyamatos áramú technikával
   A Tudomány Ünnepe (Szegedi Akadémiai Bizottság Gyógyszerészeti és Kémiai Szakbizottságának közös előadóülése), Szeged, Hungary, 8 November 2016.
7. Georgiádes Ádám
   Arilhalogenidek és acetilének réz-katalizált többlépéses in continuo átalakításai
   Patonay Tamás-Díj pályázat, Budapest, Hungary, 18 November 2016.
8. Georgiádes Ádám, Ötvös Sándor, Fülöp Ferenc:
   Arilazidok és anilinszármazékok diverzitásorientált áramlásos szintézise

MTA Heterociklusos Kémiai Munkabizottság Ülése, Balatonszemes, Hungary, 15-17 May 2017.

9. Ádám Georgiádes, Sándor B. Ötvös, Ferenc Fülöp
   Multi-step in continuo synthesis of 3,5-disubstituted pyrazoles
   XVII International Conference on Heterocycles in Bioorganic Chemistry, Galway, Ireland, 28-31 May 2017.

10. Ádám Georgiádes, Sándor B. Ötvös, Ferenc Fülöp
    Diversity-oriented synthesis of aryl azides and arylamines in a strictly controlled continuous-flow system
    18th Tetrahedron Symposium – New Developments in Organic Chemistry, Budapest, Hungary, 27-30 June 2017.

11. Sándor B. Ötvös, Ádám Georgiádes, Rebeka Mészáros, Koppány Kis, István Pálinkó, Ferenc Fülöp
    Continuous-flow oxidative homocouplings without auxiliary substances: exploiting a solid base catalyst
    18th Tetrahedron Symposium – New Developments in Organic Chemistry, Budapest, Hungary, 27-30. June 2017.

12. Georgiádes Ádám:
    Aromás azovegyületek környezettudatos előállítása áramlásos reaktorban
    A Tudomány Ünnepe (Szegedi Akadémiai Bizottság Gyógyszerészeti és Kémiai Szakbizottságának közös előadóülése), Szeged, Hungary, 9 November 2017.

13. Georgiádes Ádám:
    Alkinek értékes heterociklusokká történő többlépéses átalakítása áramlásos rendszerben
    ÚNKP Előadónap, Szeged, Hungary, 17 May 2018.

14. Georgiádes Ádám, Ozsvár Dániel, Ötvös Sándor, Fülöp Ferenc:
    3,5-Diszubsztituált pirazolok in continuo előállítása 1,3-diin intermedieren keresztül
    MTA Heterociklusos Kémiai Munkabizottság Ülése, Balatonszemes, Hungary, 6-8 June 2018.